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Review Article

Current Status and Future Directions in Graft-*Versus*-Host Disease Prevention Following Allogeneic Blood and Marrow Transplantation in Adults

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ABSTRACT

Graft-*versus*-host disease (GvHD) in its acute and chronic forms continues to represent a significant barrier to the success and wide-applicability of blood and marrow transplantation as a potentially curative treatment modality for a number of benign and malignant blood conditions. Presently, calcineurin inhibitor (CNI)-based regimens remain the most commonly used prevention strategy, although post-transplant cyclophosphamide is emerging as an alternative approach, and is providing a backbone for innovative CNI-free combinations. In this paper, we review the current strategies used for the prevention of GvHD, and highlight some of the developing and promising combinations.

1. INTRODUCTION

Allogeneic blood and marrow transplantation (BMT) is an essential therapeutic modality for the treatment of a variety of both benign and malignant hematologic conditions. Despite the implementation of various prophylactic regimens, graft-*versus*-host disease (GvHD) remains a significant contributor to the morbidity and mortality of this treatment strategy. Acute GvHD (aGvHD) continues to occur in 40% to 50% of patients, while chronic GvHD (cGvHD) affects 30% to 75% of patients [1–3]. Balancing the effect of GvHD and other factors that contribute to the outcome of allogeneic BMT has been challenging, as reducing GvHD is often offset by increased risk of graft failure, post-transplant infections and disease relapse [4,5]. Despite advances in biologic and therapeutic insights, there are currently no standardized guidelines for GvHD prophylaxis. A recent survey performed by the European Group of Blood and Marrow Transplantation (EBMT) showed marked variability in practices among institutions, emphasizing the need for developing a consensus [6]. This article aims to review the current strategies used for GvHD prevention and discuss emerging, innovative strategies.

2. BACKGROUND ON GvHD

Acute GvHD occurs when donor T-cells trigger an exaggerated inflammatory response to host-specific proteins on recipient cells [7]. The critical elements involved in this process are human leukocyte antigens (HLA), encoded by the major histocompatibility complex (MHC) and expressed on the surfaces of almost all nucleated cells. At least in the setting of calcineurin (CN)-based prophylaxis, the frequency of aGvHD directly correlates to the degree of human HLA mismatches between the donor and recipient [8,9]. However, despite HLA compatibility, aGvHD still occurs due to genetic differences, referred to as minor histocompatibility antigens, further highlighting the importance of GvHD prophylaxis, even in fully matched transplants [10].

The development of aGvHD can be divided into three phases [11,12]. In the initiation phase, an inflammatory response caused by the disease and conditioning regimen triggers the activation of antigen presenting cells (APC) [13]. The second phase is characterized by activation and expansion of host-alloreactive donor T-cells and their trafficking to the host end organs [11]. The activated T-cells subsequently begin producing and releasing inflammatory cytokines, such as interleukin-2 (IL-2) and interferon ϒ. In the final effector phase, the activated T-cells mediate cytotoxicity against host target organs. The key inflammatory cytokines involved in this phase are IL-1 and tumor necrosis factor-α (TNF-α which are produced mainly by monocytes and macrophages). These cytokines play a critical role in the propagation of a cytokine storm leading to the tissue and organ damage characteristic of aGvHD [14,15].

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The pathophysiology of cGvHD is more complex. Early inflammation causes tissue injury followed by dysregulation of B-cell and T-cell immunity that culminates in tissue repair and fibrosis. Throughout the process, B-cell signaling, T helper and cytotoxic cells 17 (Th17 and Tc17), T follicular helper cells (Tfh), characterized by the expression of the B-cell follicle homing receptor CXCR5, T regulatory cells (T_{regs}) and fibrosis-promoting factors each play a role in the progression of cGvHD emphasizing the complexity of this disorder (Reviewed in [16]).

3. BACKGROUND ON PREVENTION OF GvHD

The frequency of aGvHD closely correlates with the degree of HLA mismatches between the donor and the recipient. Several large-scale studies have shown that a greater degree of HLA mismatch between recipient and donor leads to a higher incidence of acute and cGvHD [17]. In addition to the structural differences in HLA, the level of expression of the mismatched antigens and cytomegalovirus (CMV) reactivation also influence the incidence GvHD. Furthermore, while the use of a female donor for male recipient has a greater effect on the incidence of chronic rather than aGvHD, total body irradiation (TBI) is associated with increased risk of acute but not cGvHD. Finally, the use of peripheral blood, as opposed bone marrow, stem cells and older recipient age are both strongly associated with an increased risk of chronic but not aGvHD [18,19]. Since many of these factors are potentially controllable, choosing the most suitable donor represents the first step toward successful prevention of GvHD.

Broad inhibition of T-cell function by using doublets of CN inhibitors (CNI) and methotrexate (MTX) or mycophenolate mofetil (MMF) has been the standard approach to GvHD prophylaxis. Post-transplant cyclophosphamide (PTC), initially introduced in haploidentical transplantation to circumvent the need for *ex vivo* T-cell depletion, has recently emerged as a valuable platform for GvHD prevention in matched-related and unrelated donor transplant. In this setting, PTC also offers a unique opportunity to develop CNI-free GvHD prevention regimens.

4. MATCHED RELATED AND UNRELATED DONOR TRANSPLANT

4.1. CNI and MTX or MMF

The standard combination of cyclosporine A (CSA) and a short course of MTX for GvHD prophylaxis established by Storb *et al.* in matched-related donor (MRD) and matched-unrelated donor (MUD) transplants has been challenged numerous times over the years [20]. The CNI and MTX combination was improved by the use of tacrolimus (TAC) over CSA in randomized trials, in patients receiving myeloablative conditioning. The incidence of grade II-IV aGvHD (31.9% *versus* 44.4%, $p = 0.01$) and extensive cGvHD ($p = 0.03$) were significantly lower with the TAC regimen compared to CSA in MRD transplants [21]. Interestingly, the group that received a TAC-based regimen had inferior relapse-free survival (RFS) and overall survival (OS), likely due to more advanced disease in this group. In MUD transplants, the results were similar, in that TAC and MTX were superior to CSA and MTX with improved grades II-IV aGvHD rates (56% *versus* 74%, $p = 0.0002$), but no difference in cGvHD rates (76% *versus* 70%, $p = 0.88$) [22]. Of note, bone marrow, as opposed to peripheral blood grafts were used in these studies, and unrelated-donor selection was based on HLA low resolution typing for loci A and B and high resolution for DRB1. Nevertheless, these findings led most centers in the United States to adopt the TAC-based regimen over CSA in MRD and MUD transplants [6].

Due to its toxicity, several investigators examined the option of replacing MTX by MMF in combination with CNIs. Hamilton *et al.* initially showed that, in MRD transplants, CSA and MMF result in decreased acute mucositis and more rapid engraftment compared to CSA and MTX, with no significant difference in the incidence of GvHD [23]. A more recent observational analysis examined four possible combinations of CSA or TAC with MTX or MMF. Following myeloablative conditioning, the CSA and MMF doublet was associated with an increased incidence of aGvHD in both MRD and MUD transplant (hazard ratio [HR] 1.65, $p < 0.01$ and HR 2.31, $p < 0.0001$, respectively), a higher treatment-related mortality (TRM) (HR 4.03, $p < 0.001$ and 2.23, $p < 0.001$, respectively) and worse OS when compared to TAC and MTX [24]. In addition, CSA and MTX were inferior to TAC and MTX in terms of rates of aGvHD and cGvHD, TRM and OS in MRD transplants, and in terms of incidence of cGvHD and rates of OS in MUD transplants. Finally, TAC and MTX resulted in a lower incidence of cGvHD and improved OS when compared to TAC and MMF in patients receiving transplants from MUD. In the context of reduced-intensity conditioning (RIC), there was no difference among the four combinations following MRD transplants [25]. However, the CSA and MMF regimen was associated with increased risk of aGvHD when compared to the TAC and MTX regimen (RR 1.78 < p 0.001) in MUD transplants. TRM was also higher in the TAC and MMF group, when compared to the TAC and MTX group (HR 1.48, $p = 0.009$).

4.2. CNI-Based Regimens and Additional Agents

Other agents have been studied by different investigators, either added to the doublet of CNI and MTX or MMF, or in combination with only TAC. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor that showed promising results in initial studies. However, a randomized clinical trial comparing TAC and MTX to TAC and sirolimus following myeloablative TBI-based conditioning regimen in MRD transplants failed to decrease the incidence of aGvHD (34% *versus* 26%, $p = 0.48$) and cGvHD (45% *versus* 53%, $p = 0.6$) [26]. There was also no difference in RFS and OS. Notably, the study was amended to exclude patients receiving busulfan-based preparative therapy after an unacceptably high rate of sinusoidal occlusive syndrome (SOS) in this group of patients. Not surprisingly, since patients received TBI and etoposide as a conditioning regimen, the incidence of acute mucositis was higher in the group receiving MTX. A separate study compared the combination of TAC and sirolimus with and without MTX following RIC, and reported no differences in the rates of aGvHD and extensive cGvHD [27].

Bortezomib, a proteasome inhibitor with multiple immunomodulatory effects, in combination with TAC and MTX led to encouraging

results following RIC and unrelated-donor transplants with one or two HLA loci mismatches. This prompted Koreth *et al.* to conduct a randomized phase II trial comparing TAC and MTX to TAC, MTX and bortezomib or TAC, sirolimus and bortezomib again following RIC and MUD or unrelated donor with one HLA locus mismatch. Bortezomib was given on days +1, +4 and +7. There was no difference among the three groups in terms of incidence of acute and cGvHD, RFS and OS [28].

Other agents that were examined in combination with CNI-based regimens include vorinostat, abatacept and maraviroc. Choi *et al.* conducted a trial combining vorinostat with TAC and MTX following myeloablative conditioning in MUD transplants. The rates of grade II-IV, III-IV aGvHD and cGvHD were 22%, 8% and 29%, respectively. It must be noted however that seventeen out of 37 patients enrolled in the study received bone marrow grafts [29]. Abatacept and maraviroc also showed promising results in early clinical trials [30–32]. As discussed below, the addition of maraviroc to TAC and MTX failed to improve outcomes in a large study, when compared to a matched control group receiving TAC and MTX.

4.3. Rabbit Anti-Thymocyte Globulin

The role Rabbit Anti-Thymocyte Globulin (rATG) in the prevention of GvHD was extensively examined in both retrospective and prospective studies. These yielded conflicting results, reflecting heterogeneous study populations, different formulations used (Fresenius—now Grafalon—or Thymoglobulin) and, more importantly, variable dose and timing of administration [33–37]. A recent meta-analysis of eight randomized trials was performed by Kumar *et al.* [38]. Overall, rATG was associated with reduction in the incidence of grades II-IV and grades III-IV aGvHD, and cGvHD. The risk ratio (RR) and 95% confidence intervals (CI) were 0.61 (CI 0.48–0.77), 0.52 (CI 0.34–.081) and 0.52 (CI 0.4–0.60), respectively. The relapse rate was increased with the use of rATG (RR 1.25, 95% CI 1.02–1.55), but there was no difference in TRM and OS. Importantly, while the use of the Fresenius formulation was associated with a reduced incidence of aGvHD, the use of either formulation resulted in reduction of the incidence of extensive cGvHD. Unfortunately, in this meta-analysis, the improved rates of aGvHD with the Fresenius formulation were contrasted with an increased rate of relapse (RR 1.34, 95% CI 1.03–1.73). Carefully designed studies are warranted to address the questions related to optimal dosing and timing of administration of rATG. Until then, the decision to use rATG must be individualized, taking into account the potential increase in the risk of relapse.

4.4. PTC-Based Regimens

CN and mTOR inhibitor-based regimens remain unsatisfactory for the prevention of GvHD based on several caveats. First, the risk of GvHD remains significant, despite the routine use of these regimens. Second, by indiscriminately suppressing T-cells, CN and mTOR inhibitors impair immune reconstitution, thus augmenting the risk of infections and impairing the graft-*versus*-tumor effect [39–41]. Third, these agents are cumbersome to use. They have multiple drug interactions and an unfavorable toxicity profile, including renal toxicity, thrombotic microangiopathy and SOS, and their efficacy is dependent on maintaining a therapeutic drug level, rendering the prescriber expertise and the patient compliance crucial [42–44]. Finally, the fact that CN and mTOR inhibitors require extended administration, often prevents the introduction of interventions designed to decrease the risk of disease relapse, such as donor lymphocyte infusion (DLI) and therapeutic small molecules.

PTC selectively depletes rapidly dividing host alloreactive T-cells while preserving more slowly dividing memory T-cells and T_{regs} (Reviewed in [45,46]). First introduced in the setting of haploidentical transplant to circumvent the need for *ex vivo* T-cell depletion, PTC administered on days +3 and +4 has proven to represent a unique platform for prevention of GvHD in the MRD and unrelated-donor setting. As a sole GvHD prophylaxis, single center and multi-institutional studies using myeloablative conditioning regimen and bone marrow as a source of stem cells in MRD and MUD donor transplants showed incidences of grade II-IV and grade III-IV aGvHD of 45%, and 15%, respectively. Notably, the incidence of cGvHD was very low at 13% [47,48]. Unfortunately, these promising results were not reproduced in trials using RIC preparative regimens and peripheral blood-derived grafts with rates of grade II-IV and grade III-IV aGvHD as high as 58% and 22%, respectively [49]. Notably, the rates of cGvHD remained low at 18%. When the authors compared the outcome of the treatment cohort to an institutional-matched control group, they reported higher incidence of aGvHD and decreased survival. This prompted investigators to revert to the addition of CN or mTOR inhibitors, with or without MMF, to PTC, reporting promising results, following preparative regimens of variable intensities and peripheral blood grafts [50–53].

Battipaglia *et al.* compared PTC to ATG in 1 HLA locus mismatched-unrelated donor BMT using registry data [54]. The authors reported similar incidence of grade II-IV acute and cGvHD. The incidence of grade III-IV aGvHD was, however, reduced (9% *versus* 19% respectively, $p < 0.4$). Patients receiving PTC also experienced higher DFS (55% *versus* 34%, respectively, $p < 0.5$) and a trend towards improved OS. A subgroup analysis showed similar results in patients receiving peripheral blood grafts. The most compelling evidence of the merits of PTC-based GvHD prevention in the setting of MRD, MUD or one HLA locus mismatched unrelated-donor transplants comes from a recent Blood and Marrow Transplant Clinical Trial Net randomized phase II trial [55]. Patients received RIC and one of three GvHD prevention regimens: TAC, MTX and bortezomib, TAC, MTX and maraviroc or PTC, TAC and MMF. Each of the three study groups was compared to a contemporary prospective control group from centers not participating in the trial receiving a standard combination of TAC and MTX. Only the group receiving PTC-based prophylaxis had better outcomes in comparison to the control group. The incidences of grade II-IV and III-IV aGvHD for the PTC group were 27% (90% CI 20%–35%) and 2% (90% CI 0%–5%), respectively. For the control group, the corresponding rates were 30% (90% CI 25%–36%) and 13% (90% CI 9%–16%), respectively. The 1-year incidence of cGvHD was similar at 28% in both groups. The 1-year GvHD- and Relapse-free survival (GRFS) rates were also superior in the PTC group (HR 0.72, 95% CI 0.54–0.94, $p = 0.044$). Despite improved GvHD rates, there was no difference in TRM, DFS and OS [55]. As a result, the PTC-based regimen is being compared to TAC and MTX in a phase III randomized clinical trial (BMT CTN 1703 NCT03959241). Additional studies are also warranted to examine the potential short and long-term toxicities associated with the use of PTC.

For the aforementioned reasons, the development of a CN and mTOR inhibitor-free GvHD prophylaxis regimen, based on PTC as a backbone, represents a potentially impactful approach. Preclinical data examining proteasome inhibitors seem to favor their combination with PTC as opposed to other agents. In an aggressive GvHD mouse model, the combination of PTC and ixazomib was associated with better animal survival than with either drug alone [56]. Furthermore, PTC prevented the expansion of donor T-cells and IL-1β surge, phenomena described after sustained post-transplant administration of proteasome inhibitors. Clinically, the combination of PTC and bortezomib was studied in the setting of RIC and MRD or MUD peripheral blood transplants [57]. PTC was given in a standard fashion and bortezomib was administered on day 0, 6 hours after the graft infusion and 72 hours thereafter. Patients receiving grafts from MUD also received rATG. GvHD prevention was completed on day +4. The rates of aGvHD grades II-IV and III-IV were 35.9% (95% CI 18.6%–53.6%) and 11.7% (95% CI 2.8%–27.5%), respectively. The rate of cGvHD was 27% (95% CI 11.4%–45.3%). The 2-year GRFS was 37.7% (95% CI 20.1%–55.3%). When compared to a registry-control group, the 1-year GRFS was 39% (95% CI 24%–54%) for the study group and 32% (95% CI 27%–38%) for the control group (HR 0.81, 90% CI 0.52–1.27, p = 0.44) (unpublished data). A follow-up large phase II study, including both myeloablative and RIC, and utilizing r-ATG in both MRD and MUD transplants is ongoing (NCT03945591).

In summary, at present, TAC plus MTX, with or without rATG should be considered the standard combination for the prevention of GvHD in MRD and MUD transplants. PTC-based approaches represent an emerging alternative that, pending ongoing randomized studies, may become the new standard of care. PTC also represents an appealing backbone for the development of CN and mTOR inhibitor-free intervention, which may have several advantages over the current strategies.

5. HAPLOIDENTICAL TRANSPLANT

5.1. T-Cell Depletion

Investigators from the University of Perugia pioneered a strategy that combines T-cell depletion with "mega-doses" of CD34+ following intensive myeloablative preparative therapy. This approach was associated with high engraftment rates of 90% to 95% and low acute and cGvHD rates at less than 10%. However, high rates of TRM, largely attributed to slow immune reconstitution and infectious complications and disease relapse remained unsatisfactory [58–60]. Consequently, a more selective $\alpha\beta$ T-cells, often combined with CD-19+ B-cell depletion, has emerged as an alternative approach. The rationale comes from pre-clinical models of GvHD demonstrating that $\alpha\beta$ T-cells, being the primary culprit in GvHD development, while $\gamma\delta$ T cells, part of innate immune system provide immunity without triggering GvHD [60,61]. In several studies, depletion of $\alpha\beta$ T-cells from the infused grafts was performed without pharmacologic GvHD prophylaxis, thus allowing $\gamma\delta$ T-cells and NK cells to provide immune reconstitution. A phase II study with $\alpha\beta$ T-cell and CD19+ B-cell depleted grafts with no pharmacologic GvHD prevention, following haploidentical transplants in children with non-malignant disorders was associated with skin-only aGvHD with no cGVHD. The rates of TRM and 2-year RFS were 9.3% and 91%, respectively [61]. These results were corroborated in another study in pediatric patients with primary immunodeficiency syndromes [62]. A multicenter retrospective analysis compared matched or mismatched unrelated donor (1–2 out of 8 loci mismatches) transplants with a CNI-based GvHD prevention regimen to haploidentical transplants with $\alpha\beta$ T-Cell depletion in children with acute leukemia. All patients received rATG, and those receiving haploidentical transplant also receive rituximab. The rates of grade II-IV and III-IV aGvHD were 35% and 6% and 44% and 18% in the matched and mismatched related donors, respectively. The corresponding rates in the haploidentical transplant group were 16% and 0%. Rates of cGvHD were 6% and 28% in the matched and mismatched-unrelated donor, and 9% in the haploidentical donor groups [63].

5.2. Pharmacologic Approaches

Since introduced by the Johns Hopkins University group, PTC has been extensively studied in haploidentical transplant following myeloablative and non-myeloablative conditioning regimens. The original studies focused on BM as source of hematopoietic cells but subsequent studies validated this strategy in peripheral blood BMT [64–68]. PTC is administered on day +3 and +4 and a CNI and MMF are started on day +5. Several studies showed that following non-myeloablative conditioning, the rates of aGvHD and cGvHD are lower in haploidentical transplant with PTC compared to MRD transplants with standard GvHD prophylaxis[64–66]. Similar rates of acute and cGvHD were reported following myeloablative preparative regimens with either strategy [67,68].

Another non-PTC approach for GvHD in haploidentical transplant is the GIAC (**g**ranulocyte-colony stimulating factor [G-CSF] stimulation of the donor, **i**ntensified immunosuppression, **A**TG and **c**ombination of peripheral blood and bone marrow) method, developed at Peking University in Beijing, China. This intense immunosuppressive regimen combines CNI, MTX and MMF with or without basiliximab [69]. Other groups have reproduced the original results with low incidence of grade II-IV and III-IV aGvHD at 24% and 5%, respectively, and cGvHD at 6%. However, the 1-year TRM was high at 36% [70]. In one study in patients with high-risk acute leukemia, the incidence of relapse in a group receiving haploidentical transplant with the GIAC approach was lower when compared to a group receiving MRD transplants (26% *versus* 49%, p = 0.008) [71].

6. UMBILICAL CORD BLOOD TRANSPLANTS

Umbilical cord blood (UCB) is another alternative donor source for those without MRD or MUD. UCB transplantation requires less stringent HLA compatibility between the donor and the recipient, and is associated with lower rates of GvHD [72–75]. Similar to MRD and MUD transplants, CNI are the backbone of the GvHD prophylaxis in UCB transplants. Historically, single agent CNI has been attempted as GvHD prophylaxis, but resulted in higher incidence of pre-engraftment immunological reactions and subsequent GvHD [76,77]. The addition of MTX or MMF to a CNI was shown to improve outcomes. MTX or MMF in combination with a CNI

Table 1 | The authors' recommendations and practice for GvHD prevention following allogeneic BMT.

Graft Source	Conditioning Intensity	GvHD Prevention		
		Standard of Care	Alternative Options	Our Practice
MRD	NMA	TAC and MTX (±rATG)	TAC and MMF (±rATG) PTC, TAC and MMF	CyBor and rATG
	RI	TAC and MTX (±rATG)	TAC and MMF (±rATG) PTC, TAC and MMF	CyBor and rATG
	MA	TAC and MTX (±rATG)	PTC, TAC and MMF	PTC, TAC and MMF
MUD	NMA	TAC and MTX (±rATG)	PTC, TAC and MMF	CyBor and rATG
	RIC	TAC and MTX (±rATG)	PTC, TAC and MMF	CyBor and rATG
	MA	TAC and MTX (±rATG)	PTC, TAC and MMF	PTC, TAC and MMF
Haploidentical donor	All	PTC, TAC and MMF	-	PTC, TAC and MMF
Cord blood	All	CNI and MMF	-	CNI and MMF

MRD: matched-related donor; MUD: matched-unrelated donor; NMA: non-myeloablative; RIC: reduced-intensity conditioning; MA: myeloablative; TAC: tacrolimus; MTX: methotrexate; rATG: rabbit anti-thymocyte globulin; PTC: post-transplant cyclophosphamide; MMF: mycophenolate mofetil; CNI: calcineurin inhibitor; CyBor: cyclophosphamide and bortezomib.

was compared in a retrospective analysis in patients receiving RIC and single unit UCB transplants [75]. The risk of aGvHD grades II-IV and grades III-IV was significantly higher with MMF in comparison to MTX with RR 1.75 ($p < 0.001$) and RR 1.97 ($p = 0.009$), respectively. The RFS and OS were similar between the two groups, but the risk of relapse was significantly lower in the MMF group (RR 0.69, $p = 0.009$) for patients with acute myelogenous leukemia with high relapse risk [78]. Notably, hematopoietic recovery was enhanced in the group receiving MMF as opposed to MTX. In a secondary analysis of a phase II study that was amended to use sirolimus and MMF instead of CSA and MMF, in RIC double UCB transplants, the change had no influence on the risk of acute and cGvHD [79]. There was also no difference between the two groups in terms of TRM, DFS and OS. Patients who received sirolimus and MMF had lower incidence of infectious complications between day +46 and +180 and fewer instances of renal failure [79].

The use of ATG in UCB transplantations has been more controversial. Some studies have demonstrated its benefit in enhancing protection from GvHD, while others have shown that it worsens OS by increasing infection and TRM rates [80–85]. Additional studies are needed to accurately assess the role of ATG in UCB transplant.

In the light of present data, our current recommendations and our practices for GvHD prevention following allogeneic BMT are summarized in Table 1, according to graft source and preparative regimen intensity.

7. CONCLUSION

The rates of acute and cGvHD remain significant following allogeneic BMT. TAC and MTX, with or without rATG, should be considered the standard GvHD prophylaxis for patients receiving MRD and MUD transplants. A PTC platform is an alternative strategy that may prove superior. Additionally, PTC represents an excellent platform for innovative strategies including CNI and mTOR-free approaches. In haploidentical transplants, PTC-based GvHD prophylaxis is also advantageous, given its simplicity of use compared to *ex vivo* T-cell depletion strategies. In UCB transplant, a CNI and MMF combination is, at present, the preferred regimen.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed to the writing and editing of the manuscript.

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